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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,797	GRABOWSKI ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-65* is/are pending in the application.

4a) Of the above claim(s) *37-50 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 02/05/2009 has been entered. Claims 1-36 and 66-68 are cancelled. Claims 37-65 are pending. Claims 37-50 and 62-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 51, 52, 56, 57 and 61 are amended. Claims 51-61 are currently under examination.

This application 10/776,797 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 02/04/2000.

Claim Objection

1. Previous objection of claim 57 under 37 CFR 1.75 as being a substantial duplicate of claim 52 is ***withdrawn*** because claims 52 and 57 have been amended.

Amended claim 52 reads as follows: The method of claim 51 wherein the cells harboring the vector secrete the biologically active lysosomal acid lipase in an amount and form capable of being taken up by other cells deficient in lysosomal acid lipase.

Amended claim 57 reads as follows: The method of claim 51 wherein the cells harboring the vector secrete biologically active lysosomal acid lipase in an amount capable of reducing atherosclerotic plaque.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 51-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 02/05/2009.*

(I) Newly added limitation "wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount" recited in claim 51 is unclear. It is unclear what the relationship between "a therapeutic amount" recited at the end of the wherein clause and the phrase "an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells" is. In other words, claim 51 as written simultaneously recites two patentably distinct amount of lysosomal acid lipase (LAL) expressed from the DNA sequences, one amount of LAL is sufficient for secretion and the other amount of LAL leads to a therapeutic effect. Claims 52-61 depend from claim 51.

(II) The phrase "substitution of amino acid Pro(-6) to Thr and Gly2 to Arg" recited in claim 61 of instant application is unclear. It is unclear what Gly2 is intended to mean and it is unclear what "(-6)" is intended to mean in the term "Pro(-6)". It is noted that there is no polypeptide sequence of any lysosomal acid lipase disclosed in the specification. Furthermore, the sign "-" usually indicates at the nucleotide sequences that are upstream of either the transcription start site or the translation start site. However, to the Examiner's best knowledge, no such nomenclature using the sign "-" can be found that refers to polypeptide sequences becasue there is no amino acid residue upstream of Met amino acid encoded by initiation codon.

Further elaboration pertaining to this issue had been documented on pages 3-4 of the office action mailed on 11/21/2007.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous rejection of claim 56 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because the claim has been amended

Claim 56 has been amended and no longer recites "lipid hydrolyzing proteins or polypeptides", which is a genus of proteins or polypeptides of which Applicant did not have possession at the time the application was filed.

New Matter

4. Claim 56 remains rejected and claim 57 is newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments filed on

02/05/2009 have been fully considered and found not persuasive. *It is noted that inclusion of claim 57 in this rejection is necessitated by claim amendments filed on 02/05/2009.*

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

(I) The amended claim 56 contains the limitation "further comprising the administration of exogenously produced lipid hydrolyzing proteins or polypeptides, contained in a pharmaceutically acceptable carrier". As amended, claim 56 requires administration of both (i) DNA encoding lysosomal acid lipase and (ii) exogenously produced lysosomal acid lipase because claim 56 is a dependent claim of 53, which in turn depends from claim 51. In other words, claim 56 require combination of gene therapy and protein therapy. The specification discloses various routes for administration of either lysosomal acid lipase or administration of nucleic acid encoding lysosomal acid lipase (See paragraphs [0053], [0059]-[0062], and [0065], US 2004/0223960, publication of instant application). The specification does not provide support for a method comprising administration of both (i) DNA encoding lysosomal acid lipase and (ii) exogenously produced lysosomal acid lipase, as required by claim 56.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not

described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Applicant argues that claim 56 has now been amended to require the administration of (i) DNA encoding lysosomal acid lipase. Claim 56 has been amended to recite "lysosomal acid lipase." (See page 6 of applicant's remarks file don 02/05/2009).

In response, Applicant's arguments filed on 02/05/2009 have been fully considered and found not persuasive. As stated in the maintained and revised rejection, the specification does not provide support for a method comprising administration of both (i) DNA encoding lysosomal acid lipase and (ii) exogenously produced lysosomal acid lipase, as required by amended claim 56.

(II) The amended claim 57 contains the limitation "in an amount capable of reducing atherosclerotic plaque". The specification does not provide any support describing the limitation "an amount capable of reducing atherosclerotic plaque" in the context of gene therapy.

Priority

The following statements have been made on page 8 of the office action mailed on 08/05/2008.

"As documented on page 16 of the Final office action mailed on 11/21/2007, this application 10/776,797 filed on 02/11/2004 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 filed 02/04/2000. It has been noted that the claims of instant application recites administration into cells a vector comprising and expressing a DNA sequence

encoding either biologically active lipid hydrolyzing protein or polypeptide (claim 51) or biologically active lysosomal acid lipase (claim 56). The provisional application 60/180,362 filed on 02/04/2000 disclosed administration of enzyme into cells, a protein therapy; however, the application 60/180,362 did not disclose administration of DNA sequences encoding said enzyme. In this regard, 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257) did disclose vectors expressing proteins. Therefore, the priority of instant application can be dated back to 02/02/2001.

The Examiner acknowledges that, as documented on page 17 of the Final office action mailed on 11/21/2007, Applicant filed Declaration under 37 C.F.R 1.131 on 08/07/2007 asserting that the conception and reduction to practice of the claimed invention dated prior to January 25, 2001, which is the effective filing date of withdrawn 102(e) rejection anticipated by Kapeller-Libermann et al. (See pages 19 of the Final office action mailed on 11/21/2007).

In the reply filed on 02/05/2009, Applicant argues that the provisional application 60/180,362 filed on 02/04/2000 states that the endogenous protein is "produced or manufactured inside the body by some type of device (biologic or other) for delivery to within or to other organs of the body." Applicant argues that this encompasses delivery of DNA for production of proteins by cells endogenously; and as such, the provisional application provides support for the pending claims, and accordingly, the priority date of the instant application should be the filing date of this provisional, February 4, 2000. (See bridging paragraph pages 6-7 of Applicant's remarks filed on 02/05/2009)

In response, Applicant's arguments filed on 02/05/2009 have been fully considered and found not persuasive. It is noted that the protein expressed from a tranegene administered into a

mammalian cell is not considered as endogenous protein as disclosed in the provisional application because the administered transgene is exogenously added to the recipient mammalian cell. The unclear statements the endogenous protein is "produced or manufactured inside the body by some type of device (biologic or other) for delivery to within or to other organs of the body" disclosed the provisional application 60/180,362 filed on 02/04/2000 fails to support the claimed subject matter, gene therapy. The Examiner maintains the position that the priority date of the claims 51-61 currently under examination is 02/02/2001, the filing date of 09/775,517, now US patent 6,849,257.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim interpretations: It is noted that independent claim 51 encompasses a method for providing biologically active lysosomal acid lipase (LAL) to mammalian cells *in vitro* and in *vivo*. The limitation "lysosomal acid lipase in an amount and form capable of being taken up by other cells deficient in lysosomal acid lipase" recited in claim 52 and the limitation "in an amount capable of reducing atherosclerotic plague" recited in claim 57 are considered as inherent capabilities/properties of the secreted lysosomal acid lipase expressed from recited

DNA sequences, which imparts no patentable weight. The "virus-like vectors" recited in claim 59 encompass any viral vector as the specification does not define what vectors are considered as virus-like vectors. These claim interpretations are applicable to the following 102(b) and 103(a) art rejections.

5. Claims 51, 52, 57, and 60 remain rejected under 35 U.S.C. 102(b) as being anticipated by **Anderson et al.** (Anderson et al., Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. *Mol Genet Metab.* 68(3):333-45, 1999). Applicant's arguments filed 02/05/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 9-10 of the office action mailed on 08/05/2008. It is noted that, upon further consideration as documented below, "as evidenced by Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11):1361-72, 2002)" has been removed from this maintained rejection,.

Amended claim 51 filed on 02/05/2009 reads as follows: A method for providing biologically active lysosomal acid lipase to mammalian cells, said method comprising administration into cells a vector comprising and expressing a DNA sequence encoding biologically active lysosomal acid lipase, and expressing the DNA sequence in said cells to produce biologically active lysosomal acid lipase capable of hydrolyzing lipids; wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount.

As noted in claim interpretations, independent claim 51 encompasses a method for providing biologically active lysosomal acid lipase to mammalian cells *in vitro* or *in vivo*.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 9-10 of the office action mailed on 08/05/2008, is reiterated below with revisions addressing claim amendments filed on 02/05/2009.

Anderson teaches DEAE-dextran mediated *in vitro* transfection of plasmid vectors containing hLAL (human lysosomal acid lipase, also known as cholesterol ester hydrolase/cholesterol esterase) cDNA encoding recombinant mutated hLAL into COS-1 cells, and the enzymatic activities of wild type hLAL and various mutated hLAL were analyzed (See Material and Methods, page 334, Figure 2 and Figure 6, Anderson et al., 1999).

With regard to the limitation LAL being a secreted protein as recited in claims 52 and 57, the limitation is considered as inherent properties of the recited lysosomal acid lipase because Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11):1361-72, 2002) teaches that LAL secreted by hepatocytes is taken up by Kupffer cells, the macrophages lining the walls of hepatic sinusoids (See second paragraph, right column, page 1364, Du et al., 2002).

With regard to newly added limitation "wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount", this limitation reads on (i) any amount of biologically active and secreted lysosomal acid lipase that has any detectable effect on the transfected mammalian cells *in vitro*. In this regard, Anderson teaches *in vitro* transfection of cDNA encoding recombinant mutated hLAL into COS-1 cells leads to increased hLAL activity in the *in vitro* transfected COS-1 cells

(See Figure 6, Anderson et al., 1999). Furthermore, secretion of the biologically active lysosomal acid lipase (LAL) is considered as inherent characteristics of hLAL. The amount secreted, additionally, is considered therapeutic as the hLAL is biologically active. Claim 51 does not indicate therapeutic for any particular disease or condition.

Thus, Anderson et al. (1999) clearly anticipates claims 51, 52, 57, and 60, of instant invention.

Applicant's arguments and response to Applicant's arguments

Applicants argues that the claims, as amended, require the production of the expression of the DNA sequence in mammalian cells to produce biologically active lysosomal acid lipase capable of hydrolyzing lipids; wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount. Applicant argues that the Anderson et al. (1999) reference merely showed that a vector could be produced that would express LAL. Applicant argues that Anderson et al. did not disclose or suggest how to make a stable system capable of expressing LAL at a level to provide for sufficient secretion that would still be therapeutic (See pages 7-8 of Applicant's remarks file don 02/05/2009).

In response, as stated in the rejection under 35 U.S.C 112 second, the newly added limitation "wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount" recited in claim 51 is unclear. Furthermore, as stated in the claim interpretations, the limitation "lysosomal acid lipase in an amount and form capable of being taken up by other cells deficient in lysosomal acid lipase" recited in claim 52 and the limitation "in an amount capable of reducing atherosclerotic

plague" recited in claim 57 are considered as inherent capabilities/properties of the secreted lysosomal acid lipase expressed from recited DNA sequences, which imparts no patentable weight. Applicant is advised that this rejection can be overcome by amending the claims to indicate the mammalian cells are *in vivo* (i.e. incorporating the limitations recited in dependent claim 55, which depends from claim 53 and 51, into independent claim 51).

6. Previous rejection of claims 51, 52 and 57-59 under 35 U.S.C. 102(b) as being anticipated by **Du et al.** (Du et al., Molecular and enzymatic analyses of lysosomal acid lipase in cholesteryl ester storage disease. *Mol Genet Metab.* 64(2):126-34, 1998), is ***withdrawn*** because the claims have been amended.

7. Previous rejection of claims 51, 52, 57-59, and 61 under 35 U.S.C. 102(b) as being anticipated by **Sheriff et al.** (Sheriff et al., Characterization of lysosomal acid lipase by site-directed mutagenesis and heterologous expression. *J Biol Chem.* 270(46):27766-72, 1995), is ***withdrawn*** because the claims have been amended.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 51, 53 and 54 remain rejected and claims 58, 59, and 61 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over **Anderson et al.** (Anderson et al., Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. *Mol Genet Metab.* 68(3):333-45, 1999) in view of **Bureau et al.** (US PGPUB 2002/0012914, publication date 01/31/2002, and PCT/FR98/01399 filed on 06/30/1998). Applicant's arguments filed 02/05/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the office action mailed on 08/05/2008. It is noted, upon further consideration, rejection of claim 55 pertaining to cells *in vivo* is withdrawn. The inclusion of claims 58, 59, and 61 is necessitated by claim amendments filed on 02/05/2009. Claims 58, 59, and 61 were previously rejected under 35 U.S.C. 102(b) as being anticipated by Sheriff et al., which is withdrawn as claim 51 has been amended (See preceding paragraph in this office action).

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 12-14 of the office action mailed on 08/05/2008, is reiterated below with revisions addressing claim amendments filed on 02/05/2009.

Anderson et al. teaches DEAE-dextran mediated *in vitro* transfection of plasmid vectors containing hLAL (human lysosomal acid lipase, also known as cholesterol ester hydrolase/cholesterol esterase) cDNA encoding recombinant mutated hLAL into COS-1 cells, and the enzymatic activities of wild type hLAL and various mutated hLAL were analyzed (See Material and Methods, page 334, and Figure 6, Anderson et al., 1999).

With regard to newly added limitation "wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount", this limitation reads on (i) any amount of biologically active and secreted lysosomal acid lipase that has any detectable effect on the transfected mammalian cells *in vitro,* and (ii) any amount of lysosomal acid lipase (LAL) gene expressed from an adenovirus that corrects the LAL deficiency in mice, as demonstrated by Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11):1361-72, 2002). In this regard, Anderson teaches *in vitro* transfection of cDNA encoding recombinant mutated hLAL into COS-1 cells leads to increased hLAL activity in the *in vitro* transfected COS-1 cells (See Figure 6, Anderson et al., 1999). Furthermore, secretion of the biologically active lysosomal acid lipase (LAL) is considered as inherent characteristics of hLAL.

With regard to the limitation "a polymorphic variant of lysosomal acid lipase with substitution of amino acid Pro(-6) to Thr and Gly2 to Arg" recited in amended claim 61, this limitation reads on any variant of lysosomal acid lipase because the phrase "substitution of amino acid Pro(-6) to Thr and Gly2 to Arg" is unclear as discussed in the rejection under 35 U.S.C. 112 second paragraph.

Anderson et al. does not teach **(i)** transfected cells are atheromatous plaque cells or cells of liver as recited in claim 53, and **(ii)** viral vectors recited in claim 58 and 59.

However, Bureau et al. teaches that lysosomal acid lipase is a gene associated with lysosomal deficiency in liver metabolism (See paragraphs [0009] and [0074]). Bureau et al.

specifically teaches **(i)** transfection of plasmid DNA or viral vector, including adenovirus and adeno-associated virus, alone or in combination with agents vectors in a composition comprising pharmaceutical acceptable excipients into liver tissue (See paragraphs [0002], [0009], [0024], and claim 19), and **(ii)** an improved method for enhancing electro-transferring nucleic acids that encode therapeutic proteins such as enzymes, cytokines, and hormones, into multi-celled eukaryotic organism cells *in vivo* or *in vitro* (See abstract and paragraphs [0001], [0039]-[0045], Example 10, Bureau et al., 2002).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Anderson et al. regarding transfection of vectors containing hLAL into COS-1 cells with the teachings of Bureau et al. regarding improved methods for transferring nucleic acids combined with protein products into multi-celled eukaryotic organism cells, such as cells of liver *in vitro* that metabolize lipids involving enzymatic activity of LAL, to arrive at the claimed methods for providing biologically active lysosomal acid lipase in liver cells *in vitro* as recited in claims 53 and 54, and viral vector recited in claims 58 and 59 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Anderson et al. with the teachings of Bureau et al. because the methods taught by Bureau et al. improve the efficiency for delivery of nucleic acid alone or nucleic acid combined with its encoded protein products to targeted cells *in vitro* by electro-transfer.

There would have been a reasonable expectation of success given (i) successful transfection and expression of hLAL in COS-1 cell by the teachings of Anderson et al., and (ii)

enhanced delivery of DNA into cells of various tumor cell lines via electro-transfer by the teachings of Bureau et al. (See for instance, Examples 6-8, Bureau et al.).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and response to Applicant's arguments

Applicants argues that the instant invention is entitled to a priority of invention date which is earlier than February 4, 2000 for at least the reasons described above and in the previously filed responses and declaration. Applicant argues that, as such, the Bureau et al. reference cannot be prior art to the instant invention and the rejections under 103(a) are rendered moot and should be withdrawn. Applicants assert that this does not imply the date of invention was not earlier than the provisional date.

In response, as stated in this office action under ***Priority*** section, the Examiner maintains the position that the priority date of the claims 51-61 currently under examination is 02/02/2001, the filing date of 09/775,517, now US patent 6,849,257. Furthermore, the PCT/FR98/01399 of **Bureau et al.** (US PGPUB 2002/0012914, publication date 01/31/2002) was filed on 06/30/1998 and the non-provisional application No. 60/067,487 was filed on 12/01/1997. Therefore Bureau has an earlier effective filing date than the present application. As such Bureau is proper for use under 35 U.S.C. § 103(a).

9. Claims 51, 53 and 54 remain rejected and claims 58, 59, and 61 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over **Sheriff et al.** (Sheriff et al., Characterization of lysosomal acid lipase by site-directed mutagenesis and heterologous expression. *J Biol Chem.*

270(46):27766-72, 1995) in view of **Bureau et al.** (US PGPUB 2002/0012914, publication date 01/31/2002, and PCT/FR98/01399 filed on 06/30/1998). Applicant's arguments filed 02/05/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-15 of the office action mailed on 08/05/2008. It is noted, upon further consideration, rejection of claim 55 pertaining to cells *in vivo* is withdrawn. The inclusion of claims 58, 59, 61 is necessitated by claim amendments filed on 02/05/2009. Claims 58, 59 and 61 were previously rejected under 35 U.S.C. 102(b) as being anticipated by Sheriff et al., which is withdrawn as claim 51 has been amended (See preceding paragraph in this office action).

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 14-15 of the office action mailed on 08/05/2008, is reiterated below with revisions addressing claim amendments filed on 02/05/2009.

Sheriff et al. teaches that the coding region of hLAL generated by polymerase chain reaction was cloned in a baculovirus vector, liposomes were used for initial cotransfections into Sf9 insect cells, and hLAL expression was monitored in cell lysates and medium by immunoblot analysis and enzyme assays at 72-h post-transfection with pure recombinant virus.

With regard to newly added limitation "wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount", this limitation reads on (i) any amount of biologically active and secreted lysosomal acid lipase that has any detectable effect on the transfected mammalian cells *in vitro,*

and (ii) any amount of lysosomal acid lipase (LAL) gene expressed from an adenovirus that corrects the LAL deficiency in mice, as demonstrated by Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11):1361-72, 2002). In this regard, Sheriff et al. teaches *in vitro* transfection of cDNA encoding recombinant hLAL into Sf9 cells leads to increased hLAL activity in the *in vitro* transfected Sf9 cells (See Figure 6, Sheriff et al., 1995). Furthermore, secretion of the biologically active lysosomal acid lipase (LAL) is considered as inherent characteristics of hLAL. It is noted that the deficiency of Sheriff et al. regarding "mammalian cells" is taught by second reference Bureau et al. as discussed below.

With regard to the limitation "a polymorphic variant of lysosomal acid lipase with substitution of amino acid Pro(-6) to Thr and Gly2 to Arg" recited in amended claim 61, this limitation reads on any variant of lysosomal acid lipase because the phrase "substitution of amino acid Pro(-6) to Thr and Gly2 to Arg" is unclear as discussed in the rejection under 35 U.S.C. 112 second paragraph.

Sheriff et al. does not teach **(i)** transfected cells are atheromatous plaque cells or cells of mammalian liver cells as recited in claims 51 and 53, and **(ii)** viral vector recited in claims 58 and 59.

However, Bureau et al. teaches that lysosomal acid lipase is a gene associated with lysosomal deficiency in liver metabolism (See paragraphs [0009] and [0074]). Bureau et al. specifically teaches **(i)** transfection of plasmid DNA or viral vector, including adenovirus and adeno-associated virus, alone or in combination with agents vectors in a composition comprising pharmaceutical acceptable excipients into liver tissue (See paragraphs [0002],

[0009], [0024], and claim 19), and **(ii)** an improved method for enhancing electro-transferring nucleic acids that encode therapeutic proteins such as enzymes, cytokines, and hormones, into multi-celled eukaryotic organism cells *in vitro* (See abstract and paragraphs [0001], [0039]-[0045], Example 10, Bureau et al., 2002).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Sheriff et al. regarding transfection of vectors containing hLAL into Sf9 cells with the teachings of Bureau et al. regarding improved method for transferring nucleic acids combined with protein products into multi-celled eukaryotic organism cells, such as liver cells that metabolize lipids involving enzymatic activity of LAL, to arrive at the claimed methods for providing biologically active lysosomal acid lipase in liver cells *in vitro* as recited in claims 53 and 54, and a viral vector recited in claims 58 and 59 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Sheriff et al. with the teachings of Bureau et al. because the methods taught by Bureau et al. improve the efficiency for delivery of nucleic acid alone or nucleic acid combined with its encoded protein products to targeted cells *in vivo* by electro-transfer.

There would have been a reasonable expectation of success given (i) successful transfection and expression of hLAL in Sf9 cell by the teachings of Sheriff et al., and (ii) enhanced delivery of DNA into cells of various tumor cell lines via electro-transfer by the teachings of Bureau et al. (See for instance, Examples 6-8, Bureau et al.).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and response to Applicant's arguments are the same as the documented in the maintained rejection of claims 51, 53, 54 and claims 58, 59 and 61 been newly rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (1999) in view of Bureau et al. (US PGPUB 2002/0012914, publication date 01/31/2002, and PCT/FR98/01399 filed on 06/30/1998).

Conclusion

10. No claim is allowed. Claim 55 is free of art rejection. Claim 55, as a dependent claim of claims 53 and 51, is currently rejected under 35 USC 112 second paragraph.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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